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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,779	11/30/2001	Gerardo Castillo	PROTEO.P08	1128

7590 10/17/2005

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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,779	CASTILLO ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6-10,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6-10,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4,6-10,14 and 15* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The Art Unit of this U.S. patent application has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1649.

2. The amendment filed 7-18-05 has been entered into the record and has been fully considered.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn.

5. Claims 4, 6-10 and 14-15 are pending.

Election/Restrictions

6. Applicant's election of species d) heparan sulfate identified as reading on claims 4-10, 14-15 and 18 in the reply filed on 11-5-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

7. The claims have been amended in scope with the elected species of heparan sulfate. All claims are directed to the elected species.

Claim Objections

8. Claims 6 and 8 are objected to because of the following informalities: The verbiage is awkward. The following verbiage is suggested. Claim 6 is suggested to

read, "...wherein the co-incubation is at a molar ratio of beta-amyloid protein to heparan sulfate within a range of 1:0.5 to 1:100." Claim 8 is similarly suggested to read, "...wherein the co-incubation is at a weight ratio of beta-amyloid protein to heparan sulfate within a range of 1:0.4 to 1:100."

Claim Rejections - 35 USC ∋ 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 4, 6-10 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Snow et al., Neuron 12:219-34, Jan., 1994 (IDS 5-13-03).

Snow et al., teach amyloid plaque infusate components and in vitro incubated beta amyloid for the formation of plaques such as viewed in Figures 2 and 8. In particular the method includes incubation of 10mg/ml beta amyloid 1-40 with heparan sulfate proteoglycan (mouse perlecan 5mg/ml) and EHS HS GAG=s 5mg/ml in saline at 37 degrees Celsius for either 1 or 2 week periods, (i.e., 7 or 14 days), see in particular Figure 2 and 8, p. 222 and 230-232, Infusion Reagents and Surgical and Infusion Protocol. The relative weight and molar ratios of AB to perlecan are approximately 1:5, and 1:10-1:13 for example as noted in the surgical and infusion protocol, p. 231. The

solutions were noted to be in saline which is "in distilled water" as noted. (Abeta approx. 6kDa and HS approx. 400kDa). Hence the Snow reference is deemed to anticipate claim 4. As recited in claims 5, the sulfated macromolecule of Snow is heparan sulfate and is within the ratios of 1:0.5-1:100 or about 1:5 molar and 1:0.4-1:100 weight or about 1:8 or 1:16 as noted in the surgical infusion protocol, thus meeting the limitations of claims 6-9. As in claims 14-15 the coincubations are at least or about 7 days, 1 week and occur at 37 celsius. Thus, the reference teachings anticipate the claimed invention.

Applicants argue in the 7-18-05 response that the Snow reference is the authors work and that it is improper to cite them in the same field. Alternatively, Applicants assert that the Snow reference teaches away as it is only directed to the formation of amyloid star plaques of beta amyloid with perlecan and not of beta amyloid with heparan sulfate, such being thought to inhibit formation with reference to p. 229. Applicants argue the figures are only electron micrographs and do not show the signature star plaque configuration and refer to figures 6a, 6b and 7a for such maltese cross formations.

Applicants arguments filed 7-18-05 have been fully considered but are not persuasive. The Snow reference is considered by another as the inventive body is not the same as the references authors. Accordingly, the reference is applicable prior art. Applicants referral to p. 229 does not obviate rejection but instead acknowledges a theory whereby exogenous perlecan would compete with endogenous. The Snow reference in contrast to Applicants suggestion fully supports the data as evidenced

which shows that heparan sulfate from heparan sulfate glycosaminoglycan/perlecan catalzyze amyloid fibril formations in the form of plaques consistent with maltese cross and bifringence as noted therein especially p. 228 and Figures. Accordingly all limitations are met. The reference further evidences the composition and coincubation with heparan sulfate glycosaminoglycan which is perlecan.

11. Claims 4, 6-10 and 14-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Castillo et al., J. of Neurochem., 69:2452-2465, Dec., 1997 (IDS 5-13-03).

Castillo et al., teach coincubation of amyloid beta peptide 1-40 with heparin or heparin sulfate proteoglycan (perlecan) at a temperature of 37 degrees Celsius for 1 or 2 week periods. The ratios of AB:HS or heparin include molar ratios equivalent to 1:0.5 and 1:100 and weight ratios at 1:1 and 1:100, also inclusive of molar ratio 1:5 and weight ratio 1:8 as disclosed in the solid-phase binding immunoassay studies and thioflavin T fluorometry as disclosed in particular at p. 2454, columns 1-2 and Figures 1-8 and in particular as the assays were performed with various dilutions which correlate in the desired range, see in particular Figures 1-3. Further as in claim 4, the dilutions are noted in Tris-buffered saline at pH 7.0, see for example p. 2454-5, column 2 entitled Analysis of Abeta fibrillogenesis by Thioflavin T fluorometry. As to claim 9, Castillo et al., as set forth above does not specifically teach coincubation of a molar ratio beta amyloid:heparin at a ratio of 1:5 or coincubation of a weight ratio of beta-amyloid:heparan sulfate of 1:8 or 1:16. However, Castillo et al., do teach a range of various dilutions of beta amyloid coincubated with either heparan sulfate (perlecan) or

heparin at 10uM based on a mass of 6kDa. (Abeta approx. 6kDa and HS approx. 400kDa). Thus, the artisan would recognize based on the analysis of various concentrations and resultant binding curves as exhibited in Figures 1-8 that a molar ratio of 1:5 Aβ:heparin and a weight ration of 1:8 Aβ:heparan sulfate were within the representative ranges for binding and plaque formation as disclosed in Castillo et al., 1997. The sulfated macromolecule is heparan sulfate and in particular EHS perlecan Heparan sulfate GAG chains and thus the reference anticipates claims 5 and 18 explicitly. As noted above in the 112, second paragraph rejection, no patentable distinction is made between the source of the heparan sulfate, ie., heparan sulfate and EHS perlecan heparan sulfate and thus the exclusion is deemed to be a product by process limitation not receiving patentable weight as to the contacting step with the same product. It is further noted that the method provides for no method steps which distinguish the isolation of the heparan sulfate of the claims. Accordingly, the reference teachings anticipate the claimed invention.

Applicants argue in the 7-18-05 response that the Castillo reference is the authors work published less than one year before the priority date and that it is improper to cite it as art. Applicants alternatively argue that Castillo reports on binding studies and not on plaque formations and that p. 2461 notes that perlecan could not be made to form plaques. Applicants distinguish that not everything that binds plaques and not every plaque is the preferred maltese cross plaque exhibiting a certain pattern when stained with congo red and viewed under polarized light and an amyloid star appearance when viewed by transmission electron microscopy. Applicants further

argue Castillo teaches away at p. 2460 noting substances that inhibit maltese cross formation.

Applicants arguments filed 7-18-05 have been fully considered but are not persuasive. The Castillo reference is considered by another as the inventive body is not the same as the reference's authors. Accordingly, the reference is applicable prior art. Applicants referral to p. 2461 is perplexing as nowhere does the Examiner find a statement that perlecan could not be made to form plaques. In contrast, that same pages notes, particularly at column 2, lines 28-30, "The use of perlecan from EHS tumor in the present study may actually have been an advantage due to its notably high N-sulfate content." Moreover, the reference notes its inclusion as particularly stabilizing in plaque fibril formation and stability similar to that seen in Alzheimer's brain. Accordingly, the reference at least provides suitably spherical/fibrillar plaques. Further all requisite conditions are met with respect to the dependent claims regarding co-incubation at suitable concentrations. Accordingly, the plaques are noted to be of the proper form as they were made via the same claimed procedure. In addition applicants reference to figure 8 at p. 2460 further evidence that perlecan promoted thioflavin T positive fibrils consistent with maltese cross plaques. It is true as applicant's suggest that the authors noted, "During the !-week incubation period, AB (1 -40) alone increased fibril formation (shown by increased thioflavin T fluorescence) by 10.9- fold from 1 h to 1 week. At 1 h, Clq, C3, and perlecan were significant enhancers of AB (1 - 40) fibril formation. At 1 and 3 days, only perlecan significantly increased AB (1 -40) fibril formation, whereas ApoE, al-antichymotrypsin, Clq (only at 1 day) , C3, and P

component (only at 1 day) were effective inhibitors. At 1 week, perlecan had no further significant effect on AB (1 -40) fibril formation, whereas all of the other am/oid plaque components (except P component) were inhibitory. *p < 0.05*, **p < Q.01* *** < 0 001." Accordingly the reference does not teach away from the claimed invention.

Status of Claims

12. No claims are allowed.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
October 13, 2005

SHARON TURNER, PH.D.
SHARON TURNER, PH.D.
PRIMARY EXAMINER
10-13-05